STUDIES IN NEW ANTICONVULSANTS*

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Introduction

Approximately ten years ago, while working with Dr. Tracy J. Putnam in Boston, the conclusion was reached that all of the physiological and biochemical studies which had been made up to that time on patients with seizures, had not brought us to the solution of the problem of the causation of seizures; nor had these studies resulted in any significant advances in our methods of controlling or reducing the number of seizures in patients with symptomatic or idiopathic epilepsy. In fact, there had been no progress in the medical treatment of patients with seizures since 1912 when Hauptmann introduced the use of phenobarbital. It was, therefore, decided to approach the problem from a different angle by making a systematic study of the anticonvulsant activity of a large number of chemical compounds.

Methods: The method of testing the anticonvulsant action of a compound which was in general use at that time, namely, protection against convulsant drugs, was cumbersome, costly, and unreliable. In addition, it was thought that the convulsions resulting from electrical stimulation of the cerebral cortex were physiologically more closely related to the spontaneous convulsions in humans than those produced by convulsant drugs. An apparatus[1] was devised by which a direct current could be passed through the head, between two electrodes, one of which was placed on top of the skull and the other in the animal's mouth. Cats were selected for test subjects because of their availability and the convenience in handling. It was shown that the amount of current, as measured in milliamperes, necessary to produce a convulsion in a given animal, was remarkably constant on repeated testing during one day or on different days. It was also shown that drugs, such as phenobarbital or bromides, which were known to reduce the frequency of seizures

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in many patients with epilepsy, were effective in raising the convulsive threshold to electrical stimulation in cats. Conversely, it was also shown that a procedure which increased the frequency of seizures in epileptics, such as excessive hydration by the exhibition of pitressin parenterally and water by mouth, caused a lowering of the threshold to the electrical stimulation in the animals.

A number of chemical compounds were selected for testing on the basis of the similarity of their structural formulae to that of known anticonvulsants. Various pharmaceutical manufacturers also were invited to submit for testing all compounds which could conceivably have an anticonvulsant action.

By this method, it was possible to make a preliminary screening[2] of a large number of compounds (over 700). A few of the compounds which were found to have a high degree of protective action against electrically induced convulsions, were selected for further studies in animals to determine whether they could be considered suitable for clinical use in patients subject to convulsive seizures. These studies included chronic tests in animals to determine whether continued daily administration of the compound would result in a maintenance of a high level of resistance to electrically induced convulsions and administration of the compound to various animals (mice, cats and dogs) for periods of several months to determine whether toxic changes would result from long continued administration.

Results: Approximately 10 per cent of the 700 compounds were found to produce a significant elevation of the convulsive threshold in the acute experiments (Table I). While it has not been possible to determine the exact chemical radical or radicals which are effective in raising the convulsive threshold, the effective compounds fell into six main groups: barbiturates, benzoxazoles, hydantoins, ketones, oxazolidinediones, and phenyl compounds with sulphur.

Unfortunately the laborious and time consuming nature of the preliminary testings and the toxic properties and unpalatable taste of some of the compounds have made it impossible to carry out clinical tests, up to the present time, on more than a few of these compounds, and in only one, 5,5 diphenylhydantoin, has this clinical trial been extensive. This is due, in part, to the fact that the results obtained with this compound, which was one of the first to receive a clinical trial, were so superior to the results obtained with previous forms of medical treat-

TABLE I

LIST OF COMPOUNDS HAVING A HIGH DEGREE OF ANTICONVULSANT ACTIVITY IN ANIMALS

BARBITURATES

5-n-Butyl-5-phenylbarbiturate, sodium
Ethyl i-amyl barbital
5-Phenyl-5-ethyl barbital
5-n-Propyl-5-n-butyl-thiomethyl barbituric acid
Sodium cyclopentenyl allyl barbituric acid

BENZOXAZOLES

1-Benzylbenzoxazole
1-Methylbenzoxazole
2-(α-n-Propyl-β-phenoxy)-butyl-benzoxazole

HYDANTOINS

5-i-Amoxymethyl-5-phenylhydantoin
5-(n-Butoxymethyl)-5-phenylhydantoin
5-(i-Butoxymethyl)-5-phenylhydantoin
5-(t-Butoxymethyl)-5-phenylhydantoin
5-n-Butyl-5-(1-naphthyl)-hydantoin
5-i-Butyl-5-(1-naphthyl) hydantoin
5-Cyclobutyl-5-cyclohexyl hydantoin
5-Cyclobutyl-5-phenyl-hydantoin
5,5-Diphenylhydantoin
5,5-Di(α-thienyl)-hydantoin
5-Ethyl-5-(1-naphthyl) hydantoin
5-Ethyl-5-(2-naphthyl) hydantoin
5-(1-ethylpropoxymethyl) -5-phenylhydantoin
5-Methoxymethyl-5-phenylhydantoin
5-(2-Methyl-butoxymethyl) -5-phenylhydantoin
3-Methyl-5-ethoxymethyl-5-phenylhydantoin
5-Methyl-5-(1-naphthyl)-hydantoin
5-Methyl-5-phenoxymethyl-hydantoin
5-Methyl-5-phenylhydantoin
3-Methyl-5-n-propoxy-methyl-5-phenylhydantoin
3-Methyl-5-i-propoxy-methyl-5-phenyl-hydantoin
5-(1-Naphthyl)-5-n-propylhydantoin
5-Phenyl-5-(benzyl-mercapto-methyl) hydantoin
5-Phenyl-5-i-butyl hydantoin
5-Phenyl-5-n-butyl-mercapto-methylhydantoin
5-Phenyl-5-i-butyl-sulfono-methylhydantoin
5-Phenyl-5-cyclohexyl-mercapto-methyl-hydantoin
5-Phenyl-5-(1, 2-dimethyl-propoxy-methyl) hydantoin
5-Phenyl-5-ethyl-mercapto-methylhydantoin
5-Phenyl-5-methyl-sulfono-methylhydantoin
5-Phenyl-5-methyl-mercapto-methylhydantoin
5-Phenyl-5-n-propyl-hydantoin
5-Phenyl-5-i-propyl-hydantoin
5-Phenyl-5-n-propyl-mercapto-methylhydantoin
5-i-Propoxymethyl-5-phenylhydantoin
5-n-Propyl-5-(1-naphthyl) hydantoin
Sodium 5-ethyl-5-i-amylhydantoinate
Sodium 5-phenyl-5-phenethyl hydantoinate
Sodium-5-phenyl-5-(tetrahydropyrane-4) hydantoinate
Sodium 5-(n-propoxymethyl)-5-phenyl hydantoinate
α-Tetralonespirohydantoin

KETONES

Acetophenone
Acetophenone oxime
Acetylbenzoyl
α-Benzoin oxime
Benzoylacetone
Benzyl carbamate
Benzy methyl ketone
Benzyl methyl ketone oxime
Dibenzyl ketone
Diethyl ketone
β-Dimethylaminoethyl-2-naphthyl ketone hydrochloride hydrate
2-Furyl phenyl ketone
p-Hydroxyacetophenone
Paraldehyde
Phenyl n-amyl ketone
Phenyl n-butyl ketone
Phenyl propyl ketone
Propiophenone
i-Valerophenone

OXAZOLIDINEDIONES

5,5-Diphenyl-2,4-oxazolidinedione
5,5-Di-n-propyl-2,4-oxazolidinedione calcium

PHENYL COMPOUNDS WITH SULFUR

α-(o-Aminobenzenesulfonamido)-pyridine
2,4-Diaminothiazolyl phenyl sulfone
Ethyl phenyl sulfone
Ethyl phenyl sulfoxide
Ethyl phenyl sulfide
Propyl phenyl sulfoxide
i-Propyl phenyl sulfoxide

ment, that it has been the custom to administer other compounds only to those patients whose seizures were not relieved by 5,5 diphenylhydantoin. This procedure does not give a true index of the clinical anticonvulsant activity of the other compounds but rather measures their effectivity in patients who have been refractive to 5,5 diphenylhydantoin and also to previous forms of therapy, including phenobarbital, mebaral and the bromides. This procedure was considered justifiable, however, since the object of the study was to find the most efficient anticonvulsant, and not merely a substitute for a previously established anticonvulsant. The study is still in progress and new compounds are being tested as soon as the chronic toxicity studies indicate that they are suitable and pharmacological methods of large scale production are available. This report will deal with only those compounds which have been given a fairly extensive trial to date.

5,5 Diphenylhydantoin:* The results obtained in the treatment of 200 patients with sodium 5,5 diphenylhydantoinate (dilantin sodium, phenytoin sodium) were reported to the American Medical Association at their meeting in 1938 by one of the authors and Dr. Tracy J. Putnam.[3] Further experience with this compound in a large series, was reported in 1940[4] and 1942[5]. The efficacy of sodium 5,5 diphenylhydantoinate in preventing convulsive seizures in humans, has been confirmed by many observers[6] and it is now generally recognized that it is the most effective agent for the prevention of grand mal and psychomotor seizures that is available at the present time.

In spite of the excellent results which have been obtained with sodium 5,5 diphenylhydantoinate in grand mal and psychomotor attacks, it does not have any appreciable effect on petit mal or prevent the occurrence of grand mal or psychomotor seizures in all patients. In addition, the administration of an effective dose is not possible in some instances due to the development of untoward side reactions (ataxia, nystagmus, gastric distress, skin rashes and hypertrophy of the gums).

5 Methyl, 5 Phenyl Hydantoin:* 5 methyl, 5 phenyl hydantoin was administered to forty-one patients for periods ranging from five days to one year. All of these patients had previosuly been treated with various anticonvulsant drugs, including 5,5 diphenylhydantoin, phenobarbital and mebaral, either alone or in combination and they had not been re-

* The toxicity studies on this compound were made in the laboratories of Parke, Davis & Company. We are greatly indebted to them for supplying us with the drug used in this study.

TABLE II

CLINICAL RESULTS OBTAINED BY THE ORAL ADMINISTRATION OF 5-METHYL-5-PHENYLHYDANTOIN TO 41 PATIENTS WITH CONVULSIVE SEIZURES

	Number of Patients
Entirely Controlled	9
Reduced in Frequency	10
Increased in Frequency	1
Frequency Unchanged	6
Insufficient Observation	15*

* In the majority of these patients, treatment was discontinued after a few days because of skin rash.

lieved of their seizures by these forms of medication.

This compound was administered to twenty-six of the forty-one patients for a sufficiently long period to evaluate its anticonvulsive activity. The attacks were entirely controlled in nine (35 per cent), reduced in frequency in ten (38 per cent), unchanged in six (23 per cent), and increased in frequency in one (4 per cent) (Table II). In the remaining fifteen patients, the anticonvulsant activity of the compound could not be evaluated because of the occurrence of an allergic dermatitis in fourteen and gastrointestinal symptoms in one patient.

With regard to the type of seizures, the beneficial effect of this compound was greatest when the seizures were of the grand mal or psychomotor type. The compound was administered to only a few patients with petit mal seizures and in one of these, the attacks were increased in frequency.

A skin rash developed in fourteen of the forty-one patients (34 per cent). In twelve of the fourteen patients with this reaction, the rash was of a scarlatiniform or morbilliform nature and appeared five to ten days after starting the treatment. The rash recurred with readministation of the drug in all but one case. In two patients the rash took the form of an exfoliative dermatitis which appeared after about ten days of use of the drug. In one of these patients there was also a severe eosinophilic reaction in the blood with displacement of the red cells in the bone marrow and a severe anemia. There were no fatalities and no

TABLE III

CLINICAL RESULTS OBTAINED BY THE ORAL ADMINISTRATION OF 5-i-PROPOXYMETHYL-5-PHENYLHYDANTOIN TO 25 PATIENTS WITH CONVULSIVE SEIZURES

	Number of Patients
Transient Reduction of Frequency of Seizures	5
Frequency Unchanged	20

other serious side reactions encountered with the use of the drug in doses varying from 0.4 to 1.0 gram daily, with the exception of a mild degree of gastric distress in three patients. In particular, there was no hypnotic action, ataxia or gingival hyperplasia.

The results obtained with the administration of 5 methyl, 5 phenyl hydantoin, indicate that it has an anticonvulsant activity equal, or superior to that of 5,5 diphenylhydantoin or phenobarbital since the seizures were either controlled or reduced in frequency in nineteen of the twenty-six patients (73 per cent), who had previously been treated with the latter drugs.

It is evident that this compound merits further trial, particularly if it can be prepared in a form which can be administered without so high an incidence of allergic skin reactions.

5-Isopropoxymethyl-5-phenylhydantoin:* This compound[7] was administered for periods varying from one to three months' duration to twenty-five patients (Table III) whose seizures were not controlled by phenobarbital and 5,5 diphenylhydantoin. The administration of this compound did not result in any significant change in the frequency of seizures, either when it was administered alone or in combination with their previous forms of therapy. There was a transient reduction in the frequency of the attacks in a few patients but this improvement was not maintained. There were no toxic side effects noted from the administration of this compound in dosages varying from 0.4 to 2.0 grams daily in this small number of patients. Hypertrophy of the gums, which was present in one patient previously receiving 5,5 diphenylhydantoin, receded while the 5-isopropoxymethyl-5-phenylhydantoin was being administered.

* The toxicity studies on this compound were made in the laboratories of Parke, Davis & Company. We are greatly indebted to them for supplying us with the drug used in this study.

TABLE IV

CLINICAL RESULTS OBTAINED BY THE ORAL ADMINISTRATION OF 5,5 DIPHENYLENE HYDANTOIN TO 43 PATIENTS WITH CONVULSIVE SEIZURES

	Number of Patients
Entirely Controlled	5
Reduced in Frequency	7
Frequency Unchanged	24
Insufficient Observation	7

5,5 Diphenylene Hydantoin:* 5,5 diphenylene hydantoin (diphenylene diimide; diphenylene glycolyl urea) was given to forty-three patients with convulsive seizures for a period varying from two weeks to thirty-five months (average six months). The anticonvulsant activity could be evaluated in thirty-six of these patients. In the remaining seven patients it was not possible to estimate accurately the anticonvulsant effect of the compound either because prolonged administration was prevented by the appearance of a toxic skin reaction or because follow-up data were inadequate or unreliable.

In thirty-one of the thirty-six patients, seizures had not been controlled by various other forms of therapy and in five, the 5,5 diphenylene hydantoin was the first form of therapy. The results obtained in these five patients, plus the thirty-one patients refractory to other forms of therapy, are shown in Table IV.

In the thirty-one patients who had been treated with phenobarbital and dilantin, the attacks were entirely controlled in three (8 per cent), greatly reduced in frequency in five (14 per cent), and not significantly affected in twenty-three (78 per cent). The reduction in frequency of attacks, when present, was in grand mal or psychomotor equivalent attacks. No effect was noted in the frequency of petit mal attacks in the three patients in this group who were subject to this type of attack.

In the five patients who had not received any adequate treatment previously, there was complete remission of attacks in two (both of whom had frequent petit mal and grand mal attacks) and great reduction of the frequency in an additional two. In the remaining case, there

* The toxicity studies on this compound were made in the laboratories of The Wm. S. Merrell Company. We are greatly indebted to them for supplying us with the drug used in this study.

was a temporary remission in the attacks with later recurrence at their previous frequency. All five of these patients had frequent attacks and were treated with 5,5 diphenylene hydantoin for seven months or more.

The dosage administered varied between 0.4 and 2.3 grams daily. The effects of excessive dosage were similar to those seen with mild dilantin intoxication: ataxia, nystagmus, diplopia and dysarthria, without drowsiness. The majority of adults were able to take 1.7 gm. daily (the usual maximum dose) without developing these symptoms, although an occasional patient could not. One patient took 2.3 gm. daily regularly for months without ill effect.

Seven patients of the forty-three (16 per cent) developed an allergic dermatitis while taking 5,5 diphenylene hydantoin and in one patient this diagnosis was made but was later considered doubtful. The time of onset of the rash varied from eight to twenty-one days after the first dose (average ten days). The rash was usually morbilliform, occasionally scarlatiniform, and was often accompanied by fever, headache, malaise, nausea and vomiting. No patient developed exfoliative dermatitis. In four of the seven patients, administration of 5,5 diphenylene hydantoin was resumed after the rash had disappeared. Three of these four patients were then able to continue taking 5,5 diphenylene hydantoin regularly and in adequate dosage without further difficulty, while in the other patient there was prompt reappearance of toxic symptoms necessitating withdrawal of the drug again. No patients died from any cause while taking 5,5 diphenylene hydantoin.

From our limited experience with this compound, it was concluded that it had a definite anticonvulsant activity but that it was not clearly superior to phenobarbital and 5,5 diphenyl hydantoin in refractory cases. In order to determine better its anticonvulsant efficacy in comparison to phenobarbital or 5,5 diphenyl hydantoin, it should be tested in a larger group of patients not previously shown to be refractory to those drugs. The compound has no hypnotic action and the toxic side effects of the drug are not serious although the incidence of allergic dermatitis is relatively high.

*Ethyl Phenyl Sulfone**. Twenty-five patients were given ethyl phenyl sulfone[8] for periods varying from one week to seven months. All patients had been previously treated with adequate doses of pheno-

* The toxicity studies on this compound were made in the laboratories of Parke, Davis & Company. We are greatly indebted to them for supplying us with the drug used in this study.

TABLE V

CLINICAL RESULTS OBTAINED BY THE ORAL ADMINISTRATION OF ETHYL PHENYL SULFONE TO 25 PATIENTS WITH CONVULSIVE SEIZURES

	Number of Patients
Frequency Reduced	4
Frequency Unchanged	21

barbital or 5,5 diphenylhydantoin alone, or in combination. The effects of administration of this compound are shown in Table V. There was a reduction in the frequency of attacks in four, and no appreciable change in frequency in twenty-one. Complete relief from attacks was not obtained in any of the twenty-five patients, although a combination of ethyl phenyl sulfone, and 5,5 diphenylhydantoin or phenobarbital was tried in seventeen of the twenty-five patients.

There were no significant toxic side effects from the administration of ethyl phenyl sulfone in the dosages used, i.e., 0.6 to 1.6 grams daily. In three patients there was a slight degree of ataxia when taking over 1.0 gram daily.

SUMMARY

Over 700 chemical compounds have been tested for anticonvulsant activity in animals. Approximately 10 per cent of these demonstrated a high degree of anticonvulsant activity by these tests.

Only a few of these compounds have been given a clinical trial in patients with convulsive seizures. One of these, 5,5 diphenylhydantoin, has proved to be the most effective anticonvulsant yet discovered. None of the remaining compounds which has been given a clinical trial has proved superior to 5,5 diphenylhydantoin, with the possible exception of 5 methyl, 5 phenylhydantoin. This latter compound is not as yet suitable for general use on account of its toxic side effects.

Additional chemical compounds are being tested for their anticonvulsant activity in animals, and a clinical study of a larger number of those compounds which have an anticonvulsant activity in animals is in progress.

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